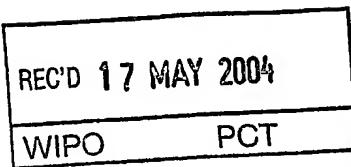




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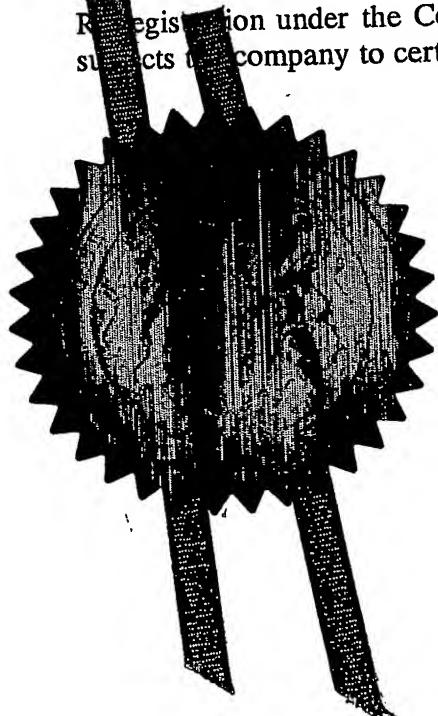


I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

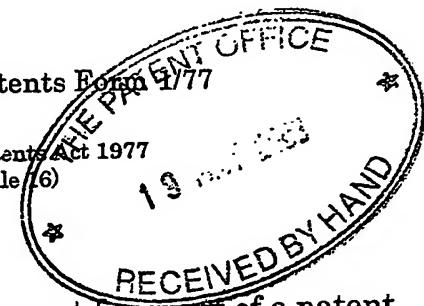
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Signed

Dated 20 February 2004



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P01/7700 0.00-0311462.6

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

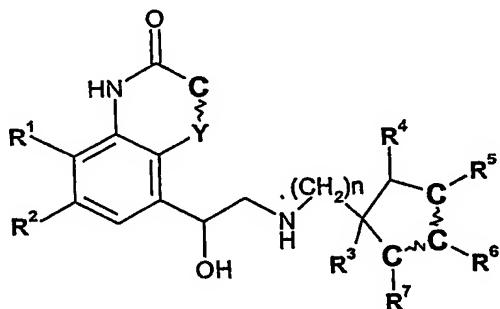
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1. Your reference	4-33206P1/HO 79		
2. Patent application number (The Patent Office will fill in this part)	19 MAY 2003 0311462.6		
3. Full name, address and postcode of the or of each applicant (underline all surnames)	NOVARTIS AG LICHTSTRASSE 35 4056 BASEL SWITZERLAND		
Patent ADP number (if you know it) If the applicant is a corporate body, give the country/state of its incorporation SWITZERLAND 7125487005			
4. Title of invention	Organic Compounds		
5. Name of your agent (if you have one)	B.A. YORKE & CO. CHARTERED PATENT AGENTS COOMB HOUSE, 7 ST. JOHN'S ROAD ISLEWORTH MIDDLESEX TW7 6NH		
6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and (if you know it) the or each application number	Country	Priority application number (if you know it)	Date of filing (day/month/year)
7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application	Date of filing (day/month/year)	
8. Is a statement of inventorship and of right to grant of a patent required in support of this request? (Answer 'Yes' if: a) any applicant named in part 3 is not an inventor; or b) there is an inventor who is not named as an applicant; or c) any named applicant is a corporate body. (see note (d))	Yes		

ORGANIC COMPOUNDS

This invention relates to organic compounds, their preparation and use as pharmaceuticals.

The invention provides in one aspect a compound of formula I



I

in free or salt or solvate form, where

-C~Y- denotes $-\text{CH}=\text{CH}-$, $-\text{CH}_2\text{-CH}_2-$ or $-\text{CH}_2\text{-O}-$;

C~C denotes $\text{C}=\text{C}$ or $\text{CH}\text{-CH}$;

one of R^1 and R^2 is hydroxy and the other is hydrogen;

n is an integer from 0 to 4;

R^3 is hydrogen or $\text{C}_1\text{-C}_{10}$ -alkyl optionally substituted by a $\text{C}_3\text{-C}_{15}$ -carbocyclic group or by

$\text{C}_1\text{-C}_{10}$ -alkoxy;

R^4 is hydrogen, hydroxy, $\text{C}_1\text{-C}_{10}$ -alkyl or $\text{C}_1\text{-C}_{10}$ -alkoxy;

R^5 and R^6 are independently hydrogen, halo, a $\text{C}_3\text{-C}_{15}$ -carbocyclic group, a 5- or 6-membered heterocyclic ring wherein at least one of the ring atoms is nitrogen, oxygen or sulphur, $\text{C}_1\text{-C}_{10}$ -alkyl optionally substituted by a $\text{C}_3\text{-C}_{15}$ -carbocyclic group, or $\text{C}_1\text{-C}_{10}$ -alkoxy optionally substituted by a $\text{C}_3\text{-C}_{15}$ -carbocyclic group,

or R^5 and R^6 together form a $\text{C}_3\text{-C}_{10}$ -cycloalkyl or $\text{C}_3\text{-C}_{10}$ -cycloalkenyl in either case

optionally substituted by $\text{C}_1\text{-C}_{10}$ -alkyl or $\text{C}_1\text{-C}_{10}$ -alkoxy; and

R^7 is hydrogen, hydroxy, a $\text{C}_3\text{-C}_{15}$ -carbocyclic group, $\text{C}_1\text{-C}_{10}$ -alkyl optionally substituted by a $\text{C}_3\text{-C}_{15}$ -carbocyclic group, or $\text{C}_1\text{-C}_{10}$ -alkoxy optionally substituted by a $\text{C}_3\text{-C}_{15}$ -carbocyclic group.

Terms used in this specification have the following meanings:

"Optionally substituted" as used herein means the group referred to can be substituted at one or more positions by any one or any combination of the radicals listed thereafter.

"C₁-C₁₀-alkyl" as used herein denotes straight chain or branched alkyl, which may be, for example, C₁ to C₁₀ alkyl such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, straight or branched pentyl, straight or branched hexyl, straight or branched heptyl, straight or branched octyl, straight or branched nonyl or straight or branched decyl. Preferably C₁-C₁₀-alkyl is C₁-C₄-alkyl.

"C₁-C₁₀-alkoxy" as used herein denotes straight chain or branched alkoxy and may be, for example, C₁ to C₁₀ alkoxy such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy, or straight or branched pentoxy, hexyloxy, heptyloxy, octyloxy, nonyloxy or decyloxy. Preferably C₁-C₁₀-alkoxy is C₁-C₄-alkoxy.

"C₃-C₁₀-cycloalkyl" as used herein denotes cycloalkyl having 3 to 10 ring carbon atoms, for example a monocyclic group such as a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl or cyclodecyl, any of which can be substituted by one or more, usually one or two, C₁-C₄-alkyl groups, or a bicyclic group such as bicycloheptyl or bicyclooctyl. Preferably C₃-C₁₀-cycloalkyl is C₃-C₆-cycloalkyl, for example cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

"C₃-C₁₀-cycloalkenyl" as used herein denotes a monovalent hydrocarbon cyclic group that contains 3 to 10 ring carbon atoms and at least one but no more than two carbon-carbon double bonds, for example a monocyclic group such as a cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, cyclononenyl or cyclodecenyl, any of which can be substituted by one or more, usually one or two, C₁-C₄-alkyl groups, or a bicyclic group such as bicyclohexenyl, bicycloheptenyl, bicyclooctenyl, bicyclononenyl or bicyclodecenyl. Preferably C₃-C₁₀-cycloalkenyl is C₃-C₆-cycloalkenyl, for example cyclopropenyl, cyclobutenyl, cyclopentenyl or cyclohexenyl.

"C₃-C₁₅-carbocyclic group" as used herein denotes a carbocyclic group having 3 to 15 ring carbon atoms, for example a monocyclic group, either aromatic or non-aromatic, such as a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl or phenyl, any of which can be substituted by one or more, usually one or two, C₁-C₄-alkyl groups, or a bicyclic group such as bicyclooctyl, bicyclononyl, bicyclodecyl, indanyl or indenyl, again any of which can be substituted by one or more, usually one or two, C₁-C₄-alkyl groups. Preferably the C₃-C₁₅-carbocyclic group is a C₅-C₁₀-carbocyclic group, especially for example cyclopentyl, cyclohexyl or phenyl.

"Halo" or "halogen" as used herein denotes an element belonging to group 17 (formerly group VII) of the Periodic Table of Elements, which may be, for example, fluorine, chlorine, bromine or iodine.

"5- or 6- membered heterocyclic ring containing at least one ring heteroatom selected from the group consisting of nitrogen, oxygen and sulphur" as used herein may be, for example, pyrrole, pyrrolidine, pyrazole, imidazole, triazole, tetrazole, thiadiazole, isothiazole, thiophene, oxadiazole, pyridine, oxazole, isoxazole, pyrazine, pyridazine, pyrimidine, piperazine, morpholino, triazine, oxazine or thiazole. Preferred 5- or 6- membered heterocyclic rings include thiophene, imidazole, thiazole and pyridine. The 5- or 6- membered heterocyclic ring can be unsubstituted or substituted. Preferred substituents on the heterocyclic ring include halo, cyano, hydroxy, carboxy, aminocarbonyl, nitro, C₁-C₁₀-alkyl, C₁-C₁₀-alkoxy and C₃-C₁₀-cycloalkyl. Especially preferred substituents on the ring include C₁-C₁₀-alkyl and C₁-C₁₀-alkoxy.

"C~C" denotes C=C or CH-CH. However in order to observe the maximum valence permitted "C~C~C" can be "C-C-C", "C-C=C" or "C=C-C" but not "C=C=C".

Throughout this specification and in the claims that follow, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

Preferred compounds of the present invention are compounds of formula I where
-C~Y- denotes -CH=CH-;
C-C denotes C=C or CH-CH;
one of R¹ and R² is hydroxy and the other is hydrogen;
n is 0;
R³ and R⁴ are both hydrogen;
R⁵ and R⁶ are independently hydrogen or C₁-C₁₀-alkyl,
or R⁵ and R⁶ together form a C₃-C₁₀-cycloalkyl or C₃-C₁₀-cycloalkenyl in either case
optionally substituted by C₁-C₁₀-alkyl; and
R⁷ is hydrogen, hydroxy, a C₃-C₁₅-carbocyclic group or C₁-C₁₀-alkyl optionally substituted
by a C₃-C₁₅-carbocyclic group.

Especially preferred compounds of the present invention are compounds of formula I where

-C~Y- denotes -CH=CH-;

C-C denotes C=C or CH-CH;

one of R¹ and R² is hydroxy and the other is hydrogen;

n is 0;

R³ and R⁴ are both hydrogen;

R⁵ and R⁶ are independently hydrogen or C₁-C₄-alkyl,

or R⁵ and R⁶ together form a C₃-C₆-cycloalkyl or C₃-C₆-cycloalkenyl in either case
optionally substituted by C₁-C₄-alkyl; and

R⁷ is hydrogen, hydroxy, a C₃-C₁₀-carbocyclic preferably C₃-C₆-cycloalkyl, or C₁-C₁₀-alkyl

optionally substituted by a C₃-C₁₀-carbocyclic group preferably an unsaturated C₅-C₈-
carbocyclic group.

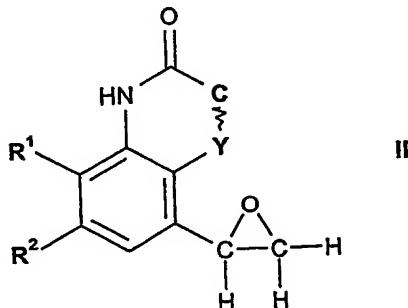
The compounds of formula (I) are capable of forming acid addition salts, particularly pharmaceutically acceptable acid addition salts. Pharmaceutically acceptable acid addition salts of the compound of formula I include those of inorganic acids, for example, hydrohalic acids such as hydrofluoric acid, hydrochloric acid, hydrobromic acid or hydroiodic acid, nitric acid, sulfuric acid, phosphoric acid; and organic acids such as formic acid, acetic acid, propionic acid, butyric acid, benzoic acid, o-hydroxybenzoic acid, p-hydroxybenzoic acid, p-chlorobenzoic acid, diphenylacetic acid, triphenylacetic acid, 1-hydroxynaphthalene-2-carboxylic acid, 3-hydroxynaphthalene-2-carboxylic acid, aliphatic hydroxy acids such as lactic acid, citric acid, tartaric acid or malic acid, dicarboxylic acids such as fumaric acid, maleic acid or succinic acid, and sulfonic acids such as methanesulfonic acid or benzenesulfonic acid. These salts may be prepared from compounds of formula I by known salt-forming procedures.

In those compounds where there is an asymmetric carbon atom the compounds exist in individual optically active isomeric forms or as mixtures thereof, e.g. as racemic or diastereomeric mixtures. The present invention embraces individual optically active R and S isomers as well as mixtures, e.g. racemic or diastereomeric mixtures, thereof.

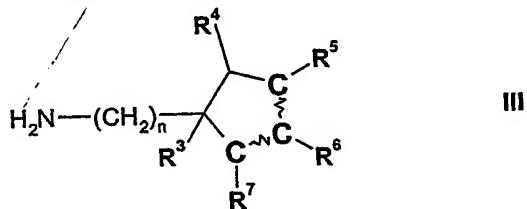
Specific especially preferred compounds of the invention are those described hereinafter in the Examples.

The present invention also provides a process for the preparation of compounds of formula I in free or salt or solvate form. They can be prepared by a process comprising:

(i) reacting a compound of formula II



or a protected form thereof wherein -C-Y-, R¹ and R² are as hereinbefore defined, with a compound of formula III



or a protected form thereof wherein C-C, R³, R⁴, R⁵, R⁶, R⁷ and n are as hereinbefore defined; and

(ii) recovering the resultant compound of formula I in free or salt or solvate form.

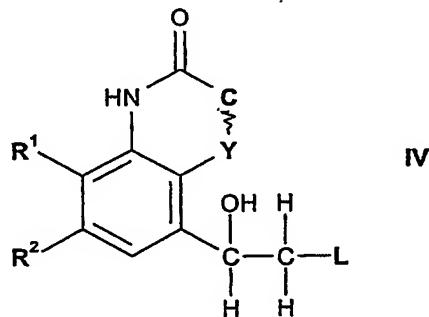
The process may be carried out using known procedures for reacting epoxides with amines or analogously as hereinafter described in the Examples. The reaction is conveniently carried out without a solvent or in an inert solvent, for example an organic solvent such as N,N'-dimethylformamide in the presence of a silylating agent such as N,O-bis(trimethylsilyl)-acetamide. The reaction temperature is conveniently from 25°C to 200°C, preferably from 80°C to 190°C. The temperature may be achieved by conventional heating or by microwave irradiation.

Compounds of formula I in free form may be converted into salt form, and vice versa, in a conventional manner. The compounds in free or salt form can be obtained in the form of hydrates or solvates containing a solvent used for crystallisation. Compounds of formula I can be recovered from reaction mixtures and purified in a conventional manner. Isomers, such as enantiomers, may be obtained in a conventional manner, e.g. by fractional

crystallisation or asymmetric synthesis from correspondingly asymmetrically substituted, e.g. optically active, starting materials.

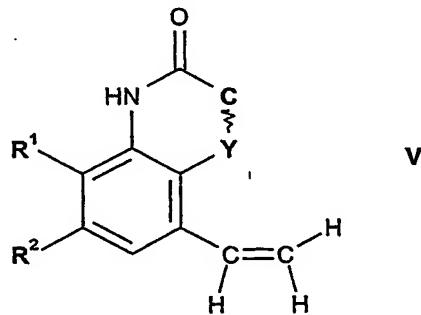
Compounds of formula II are known compounds or can be prepared by processes analogous to those used for the preparation of the known compounds, for example the procedures described in J. Med. Chem. 1987, 30, 1563.

Compounds of formula II in which the carbon atom of the epoxide ring that is attached to the phenyl group is chiral may be prepared from a compound of formula IV



or a protected form thereof where $-C \sim Y-$, R^1 and R^2 are as hereinbefore defined and L is a leaving atom or group, as described in international patent application WO 95/25104 or analogously as hereinafter described in the Examples.

Compounds of formula II may alternatively be prepared by epoxidation of a compound of formula V



or a protected form thereof where $-C \sim Y-$, R^1 and R^2 are as hereinbefore defined, using conventional procedures.

Compounds of formula III are known or may be prepared by methods analogous to those used for the preparation of the known compounds for example as described in the Examples. The amine group may be protected by known methods, for example using an amine-protective group described in Protective Groups in Organic Synthesis, T. W. Greene,

P.G.M. Wuts, John Wiley & Sons Inc, Third Edition, 1999, preferably benzyl or trifluoroacetyl.

Compounds of formula IV are known or may be prepared by methods analogous to those used for the preparation of known compounds, for example those used in the Examples hereinafter.

Compounds of formula V are known or may be prepared by known procedures.

Where desired, the protection of any reactive group may be carried out at any appropriate stage in the above processes. The protecting group is suitably one used conventionally in the art and may be introduced and removed using conventional procedure. For example, when a hydroxy group is protected by a benzyl group, the latter may be removed by catalytic hydrogenation in the presence of palladium on charcoal using conventional procedures, such as those used hereinafter in the Examples.

Compounds of formula I in free, salt or solvate form are useful as pharmaceuticals. Accordingly the invention also provides a compound of formula I in free, salt or solvate form for use as a pharmaceutical. The compounds of formula I in free, salt or solvate form, hereinafter referred to alternatively as "agents of the invention", have good β_2 -adreno-receptor agonist activity. The β_2 agonist activity, onset of action and duration of action of the agents of the invention may be tested using the guinea pig tracheal strip in vitro assay according to the procedure of R.A. Coleman and A.T. Nials, J. Pharmacol. Methods 1989, 21, 71. The binding potency and selectivity for the β_2 -adrenoreceptor relative to the β_1 -adrenoreceptor can be measured by a classical filtration binding assay according to the procedure of Current Protocols in Pharmacology (S. J. Enna (editor-in-chief) et al, John Wiley & Son, Inc, 1998), or by cAMP determination in cells expressing β_2 - or β_1 -adrenoceptor, according to the procedure of B. January et al, Brit. J. Pharmacol. 1998, 123, 701.

The agents of the invention commonly have a rapid onset of action and have a prolonged stimulating action on the β_2 -adrenoreceptor, compounds of the Examples hereinbelow having K_i (β_2) values of the order of 0.1 to 1000 nM, having durations of action of the order of 1 to greater than 12 hours. Many of the compounds have binding selectivities for the β_2 -adreno-receptor relative to the β_1 -adrenoreceptor from 1.5 to 500. The compounds of

Examples 2, 5 and 7 have β_2 and β_1 binding potencies, measured by a classical filtration binding assay, represented by K_i values (β_2/β_1) (in μM) of 0.077/0.132, 0.048/0.491 and 0.0004/0.006 respectively.

Having regard to their β_2 agonist activity, the agents of the invention are suitable for use in the treatment of any condition which is prevented or alleviated by activation of the β_2 -adrenoreceptor. In view of their long acting selective β_2 agonist activity, the agents of the invention are useful in the relaxation of bronchial smooth muscle and the relief of bronchoconstriction. Relief of bronchoconstriction can be measured in models such as the in vivo plethysmography models of Chong et al, J. Pharmacol. Toxicol. Methods 1998, 39, 163, Hammelmann et al, Am. J. Respir. Crit. Care Med., 1997, 156, 766 and analogous models. The agents of the invention are therefore useful in the treatment of obstructive or inflammatory airways diseases. In view of their long duration of action, it is possible to administer the agents of the invention once-a-day in the treatment of such diseases. In another aspect, agents of the invention commonly exhibit characteristics indicating a low incidence of side effects commonly encountered with β_2 agonists such as tachycardia, tremor and restlessness, for example as measured in the in vivo model described by Fozard et al in Pulmonary Pharmacology and Therapeutics 2001, vol. 14, 289. Such agents are accordingly suitable for use in on demand (rescue) treatment as well as prophylactic treatment of obstructive or inflammatory airways diseases.

Treatment of a disease in accordance with the invention may be symptomatic or prophylactic treatment. Inflammatory or obstructive airways diseases to which the present invention is applicable include asthma of whatever type or genesis including both intrinsic (non-allergic) asthma and extrinsic (allergic) asthma. Treatment of asthma is also to be understood as embracing treatment of subjects, e.g. of less than 4 or 5 years of age, exhibiting wheezing symptoms and diagnosed or diagnosable as "wheezing infants", an established patient category of major medical concern and now often identified as incipient or early-phase asthmatics. (For convenience this particular asthmatic condition is referred to as "wheezing-infant syndrome".)

Prophylactic efficacy in the treatment of asthma will be evidenced by reduced frequency or severity of symptomatic attack, e.g. of acute asthmatic or bronchoconstrictor attack, improvement in lung function or improved airways hyperreactivity. It may further be evidenced by reduced requirement for other, symptomatic therapy, i.e. therapy for or

intended to restrict or abort symptomatic attack when it occurs, for example anti-inflammatory (e.g. corticosteroid) or bronchodilatory. Prophylactic benefit in asthma may in particular be apparent in subjects prone to "morning dipping". "Morning dipping" is a recognised asthmatic syndrome, common to a substantial percentage of asthmatics and characterised by asthma attack, e.g. between the hours of about 4 to 6 am, i.e. at a time normally substantially distant from any previously administered symptomatic asthma therapy.

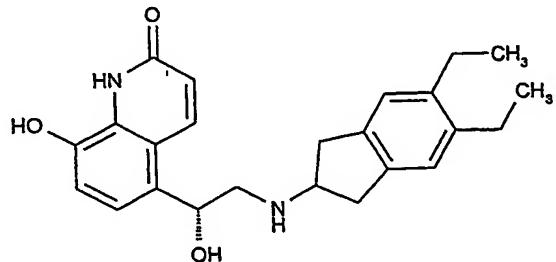
Other inflammatory or obstructive airways diseases and conditions to which the present invention is applicable include adult respiratory distress syndrome (ARDS), chronic obstructive pulmonary or airways disease (COPD or COAD), including chronic bronchitis, or dyspnea associated therewith, emphysema, as well as exacerbation of airways hyperreactivity consequent to other drug therapy, in particular other inhaled drug therapy. The invention is also applicable to the treatment of bronchitis of whatever type or genesis including, e.g., acute, arachidic, catarrhal, croupus, chronic or phthinoid bronchitis. Further inflammatory or obstructive airways diseases to which the present invention is applicable include pneumoconiosis (an inflammatory, commonly occupational, disease of the lungs, frequently accompanied by airways obstruction, whether chronic or acute, and occasioned by repeated inhalation of dusts) of whatever type or genesis, including, for example, aluminosis, anthracosis, asbestosis, chalcosis, ptilosis, siderosis, silicosis, tabacosis and byssinosis.

Having regard to their β_2 agonist activity, the agents of the invention are also useful in the treatment of a condition requiring relaxation of smooth muscle of the uterus or vascular system. They are thus useful for the prevention or alleviation of premature labour pains in pregnancy. They are also useful in the treatment of chronic and acute urticaria, psoriasis, allergic conjunctivitis, actinitis, hay fever, and mastocytosis.

The agents of the invention are also useful as co-therapeutic agents for use in combination with other drug substances such as anti-inflammatory, bronchodilatory, antihistamine or anti-tussive drug substances, particularly in the treatment of obstructive or inflammatory airways diseases such as those mentioned hereinbefore, for example as potentiators of therapeutic activity of such drugs or as a means of reducing required dosaging or potential side effects of such drugs. An agent of the invention may be mixed with the other drug substance in a fixed pharmaceutical composition or it may be administered separately,

before, simultaneously with or after the other drug substance. Accordingly the invention includes a combination of an agent of the invention as hereinbefore described with an anti-inflammatory, bronchodilatory, antihistamine or anti-tussive drug substance, said agent of the invention and said drug substance being in the same or different pharmaceutical composition. Such anti-inflammatory drugs include steroids, in particular glucocorticosteroids such as budesonide, beclamethasone dipropionate, fluticasone propionate, ciclesonide or mometasone furoate and compounds described in WO 0200679, WO 0288167, WO 0212266 and WO 02100879 (GSK); LTB4 antagonists such as those described in US 5451700 and US 5451700; LTD4 antagonists such as montelukast and zafirlukast; PDE4 inhibitors such as Ariflo® (GlaxoSmith Kline), Roflumilast (Byk Gulden), V-11294A (Napp), BAY19-8004 (Bayer), SCH-351591 (Schering-Plough), Arofylline (Almirall Prodesfarma), PD189659 (Parke-Davis), AWD-12-281 (Asta Medica), CDC-801 (Celgene), KW-4490 (Kyowa Hakko Kogyo) and those described in WO 03/022275 (Pfizer); A2a agonists such as those described in EP 1052264, EP 1241176, WO 0023457, WO 0077018, WO 0123399, WO 0160835, WO 0194368, WO 0200676, WO 0222630, WO 0296462, WO 0127130, WO 0127131, WO 9602543, WO 9602553, WO 9828319, WO 9924449, WO 9924450, WO 9924451, WO 9938877, WO 9941267, WO 9967263, WO 9967264, WO 9967265, WO 9967266, WO 9417090, EP 409595A2 and WO 0078774; and A2b antagonists such as those described in WO 02/42298. Such bronchodilatory drugs include anticholinergic or antimuscarinic agents, in particular ipratropium bromide, oxitropium bromide and tiotropium bromide.

The agents of the invention are also useful as co-therapeutic agents for use in combination with other beta-2 adrenoceptor agonists, for example as a rescue medication. Suitable beta-2 adrenoceptor agonists include salbutamol, terbutaline, salmeterol and, especially, formoterol and pharmaceutically acceptable salts thereof, and compounds (in free or salt or solvate form) of formula I of PCT International patent publication No. WO 00/75114, which document is incorporated herein by reference, preferably compounds of the Examples thereof, especially a compound of formula



and pharmaceutically acceptable salts thereof.

Co-therapeutic antihistamine drug substances include cetirizine hydrochloride, acetaminophen, clemastine fumarate, promethazine, loratadine, desloratadine, diphenhydramine and fexofenadine hydrochloride.

Combinations of agents of the invention and steroids, PDE4 inhibitors, A2a agonists, A2b antagonists or LTD4 antagonists may be used, for example, in the treatment of COPD or, particularly, asthma. Combinations of agents of the invention and anticholinergic or antimuscarinic agents, PDE4 inhibitors, A2a agonists, A2b antagonists, dopamine receptor agonists or LTB4 antagonists may be used, for example, in the treatment of asthma or, particularly, COPD.

In accordance with the foregoing, the present invention also provides a method for the treatment of an obstructive or inflammatory airways disease which comprises administering to a subject, particularly a human subject, in need thereof a compound of formula I, or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore described. In another aspect, the invention provides a compound of formula I, or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore described for use in the preparation of a medicament for the treatment of an obstructive or inflammatory airways disease.

The agents of the invention may be administered by any appropriate route, e.g. orally, for example in the form of a tablet or capsule; parenterally, for example intravenously; topically to the skin, for example in the treatment of psoriasis; intranasally, for example in the treatment of hay fever; or, preferably, by inhalation, particularly in the treatment of obstructive or inflammatory airways diseases.

In a further aspect, the invention also provides a pharmaceutical composition comprising a compound of formula I in free form or in the form of a pharmaceutically acceptable salt or solvate thereof, optionally together with a pharmaceutically acceptable diluent or carrier therefor. Such compositions may be prepared using conventional diluents or excipients and techniques known in the galenic art. Thus oral dosage forms may include tablets and capsules. Formulations for topical administration may take the form of creams, ointments, gels or transdermal delivery systems, e.g. patches. Compositions for inhalation may comprise aerosol or other atomizable formulations or dry powder formulations.

When the composition comprises an aerosol formulation, it preferably contains, for example, a hydro-fluoro-alkane (HFA) propellant such as HFA134a or HFA227 or a mixture of these, and may contain one or more co-solvents known in the art such as ethanol (up to 20% by weight), and/or one or more surfactants such as oleic acid or sorbitan trioleate, and/or one or more bulking agents such as lactose. When the composition comprises a dry powder formulation, it preferably contains, for example, the compound of formula I having a particle diameter up to 10 microns, optionally together with a diluent or carrier, such as lactose, of the desired particle size distribution and a compound that helps to protect against product performance deterioration due to moisture. When the composition comprises a nebulised formulation, it preferably contains, for example, the compound of formula I either dissolved, or suspended, in a vehicle containing water, a co-solvent such as ethanol or propylene glycol and a stabiliser, which may be a surfactant.

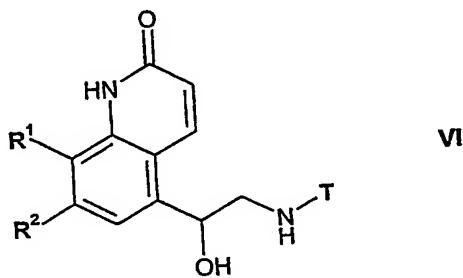
The invention also includes (A) a compound of formula I as hereinbefore described in free form, or a pharmaceutically acceptable salt or solvate thereof, in inhalable form; (B) an inhalable medicament comprising such a compound in inhalable form together with a pharmaceutically acceptable carrier in inhalable form; (C) a pharmaceutical product comprising such a compound in inhalable form in association with an inhalation device; and (D) an inhalation device containing such a compound in inhalable form.

Dosages employed in practising the invention will of course vary depending, for example, on the particular condition to be treated, the effect desired and the mode of administration. In general, suitable daily dosages for administration by inhalation are of the order of from 1 to 5000 µg.

The invention is illustrated by the following Examples.

EXAMPLES

Especially preferred compounds of formula I are also compounds of formula VI



wherein R¹, R² and T are as shown in the following table, the method of preparation being described hereinafter. All compounds are in the free form. ¹H NMR spectra are recorded at 400 MHz in CDCl₃ unless otherwise noted. Mass spectra are obtained under electrospray ionisation conditions with LC gradient elution of 5% to 95% acetonitrile-water in the presence of 0.1% formic acid.

Ex	R ¹	R ²	T	MH ⁺
1	-OH	-H		339
2	-OH	-H		395
3	-OH	-H		305
4	-OH	-H		287
5	-OH	-H		371
6	-OH	-H		357
7	-OH	-H		393
8	-H	-OH		-
9	-H	-OH		-

10	-H	-OH		-
11	-H	-OH		-
12	-H	-OH		-
13	-H	-OH		-
14	-H	-OH		-
15	-OH	-H		-
16	-OH	-H		-
17	-OH	-H		-
18	-OH	-H		-
19	-OH	-H		-
20	-OH	-H		-
21	-H	-OH		-
22	-H	-OH		-
23	-H	-OH		-
24	-H	-OH		-
25	-H	-OH		-

26	-H	-OH		-
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Example 1

8-Hydroxy-5-[R-1-hydroxy-2-(2,3,4,7-tetrahydro-1H-inden-2-ylamino)-ethyl]-1H-quinolin-2-one

(a) Liquid ammonia (80 ml) is condensed at -78°C and 2-aminoindane (2 g, 15 mmol) is added, followed by lithium wire (2 g, 300 mmol) portionwise over 5 minutes. The reaction is stirred at -78°C for 2 hours, then cautiously quenched with ethanol (100 ml) and warmed to ambient temperature overnight. Water is added, the mixture is extracted with ether and the combined organic extracts are washed with brine, dried (MgSO_4) and evaporated to afford 2,3,4,7-tetrahydro-1H-inden-2-ylamine. $[\text{M} + \text{CH}_3\text{CN}] 177$.

(b) N,O -Bis(trimethylsilyl)acetamide (0.464 ml, 1.88 mmol) is added to a solution of 2,3,4,7-tetrahydro-1H-inden-2-ylamine (0.509 g, 3.76 mmol) in N,N -dimethylformamide (DMF) (1 ml) and the mixture stirred at ambient temperature for 30 minutes. 8-Benzylxyloxy-5-R-oxiranyl-1H-quinolin-2-one (0.736 g, 2.51 mmol) is added and the mixture heated at 80°C for 4 days. The solvent is evaporated and the crude product purified by flash column chromatography (neat ethyl acetate (EtOAc) – 10% methanol- EtOAc gradient elution) to afford 8-benzylxyloxy-5-[R-1-hydroxy-2-(2,3,4,7-tetrahydro-1H-inden-2-ylamino)ethyl]-1H-quinolin-2-one, $\text{MH}^+ 443$.

(c) 10% Pd/C (20 mg) is added to a solution of 8-benzylxyloxy-5-[R-1-hydroxy-2-(2,3,4,7-tetrahydro-1H-inden-2-ylamino)ethyl]-1H-quinolin-2-one (0.212 g, 0.49 mmol) in ethanol (10 ml) and the resulting suspension stirred under 0.35 bar hydrogen atmosphere for 1 hour. The reaction mixture is filtered through a Celite™ filter plug, evaporated and purified by flash column chromatography (10:1 dichloromethane-methanol elution) to afford 8-hydroxy-5-[R-1-hydroxy-2-(2,3,4,7-tetrahydro-1H-inden-2-ylamino)-ethyl]-1H-quinolin-2-one, $\text{MH}^+ 339$.

Example 2**5-[R-2-(5,6-Diethyl-2,3,4,7-tetrahydro-1H-inden-2-ylamino)-1-hydroxyethyl]-8-hydroxy-1H-quinolin-2-one**

(a) Liquid ammonia (50 ml) is condensed at -78°C and 2-amino-5,6-diethylindane (WO 0075114; 1 g, 4.43 mmol) is added, followed by lithium wire (0.615 g, 88 mmol) portionwise over 5 minutes. The reaction is stirred at -78°C for 3 hours, then cautiously quenched with ethanol (100 ml) and warmed to ambient temperature overnight. Water is added, the mixture is extracted with ether and the combined organic extracts are washed with brine, dried (MgSO_4) and evaporated to afford 5,6-diethyl-2,3,4,7-tetrahydro-1H-inden-2-ylamine. δ_{H} 0.95 (t J 7.3 6H), 1.95-2.10 (m 2H), 2.08 (q J 4H), 2.6 (m 6H), 3.65 (m 1H)

(b) 5,6-Diethyl-2,3,4,7-tetrahydro-1H-inden-2-ylamine is reacted with 8-benzyloxy-5-R-oxiranyl-1H-quinolin-2-one using the procedure described in Example 1(b) to yield 8-benzyloxy-5-[R-2-(5,6-diethyl-2,3,4,7-tetrahydro-1H-inden-2-ylamino)-1-hydroxyethyl]-1H-quinolin-2-one, MH^+ 485.

(c) 8-Benzylxy-5-[R-2-(5,6-diethyl-2,3,4,7-tetrahydro-1H-inden-2-ylamino)-1-hydroxyethyl]-1H-quinolin-2-one is deprotected using the procedure described in Example 1(c) to yield 5-[R-2-(5,6-diethyl-2,3,4,7-tetrahydro-1H-inden-2-ylamino)-1-hydroxyethyl]-8-hydroxy-1H-quinolin-2-one, MH^+ 395.

Examples 3 and 4**8-Hydroxy-5-[R-1-hydroxy-2-(1S,2S-2-hydroxy-cyclopentylamino)ethyl]-1H-quinolin-2-one**
and 5-[R-2-(S-cyclopent-2-enylamino)-1-hydroxyethyl]-8-hydroxy-1H-quinolin-2-one

(a) A suspension of 8-benzyloxy-5-R-oxiranyl-1H-quinolin-2-one (0.20 g, 0.68 mmol) and (1S,2S)-2-benzyloxy-cyclopentylamine (0.391 g, 2.0 mmol) in CHCl_3 (0.5 ml) is heated and the solvent allowed to evaporate. The resultant melt is heated at 110°C for 16 hours and the crude product purified by reverse phase chromatography using a Jones Flashmaster Personal™ flash chromatography system with gradient elution 0-30% acetonitrile-water containing 0.1% trifluoroacetic acid to afford 8-benzyloxy-5-[R-2-(1S,2S-2-benzyloxy-cyclopentylamino)-1-hydroxyethyl]-1H-quinolin-2-one trifluoroacetate. MH^+ 485.

(b) Concentrated hydrochloric acid (1 ml) is added to a solution of 8-benzyloxy-5-[R-2-(1R,2R-2-benzyloxy-cyclopentylamino)-1-hydroxy-ethyl]-1H-quinolin-2-one trifluoroacetate (0.306 g, 0.51 mmol) in ethanol (2 ml) and the mixture is heated at reflux for 48 hours. The residue is diluted with methanol, the solvent is evaporated and the crude product is purified by reverse phase chromatography using a Jones Flashmaster Personal™ flash chromatography system with gradient elution 0-50% acetonitrile-water containing 0.1% trifluoroacetic acid to afford two products, 8-hydroxy-5-[R-1-hydroxy-2-(1S,2S-2-hydroxy-cyclopentylamino)ethyl]-1H-quinolin-2-one trifluoroacetate (MH^+ 305) and 5-[R-2-(S-cyclopent-2-enylamino)-1-hydroxyethyl]-8-hydroxy-1H-quinolin-2-one trifluoroacetate. (MH^+ 287).

Example 5

5-[R-2-(1S,2S-2-Cyclohexylcyclopentylamino)-1-hydroxyethyl]-8-hydroxy-1H-quinolin-2-one and 5-[R-2-(1R,2R-2-cyclohexylcyclopentylamino)-1-hydroxyethyl]-8-hydroxy-1H-quinolin-2-one

(a) A suspension of 8-benzyloxy-5-R-oxiranyl-1H-quinolin-2-one (0.110 g, 0.38 mmol) and (+/-) *cis*-2-cyclohexylcyclopentylamine (J. Med. Chem., 1973, 16, 679; 0.125 g, 0.76 mmol) in $CHCl_3$ (0.5 ml) is heated and the solvent allowed to evaporate. The resultant melt is heated at 80°C for 24 hours and the crude product purified by reverse phase chromatography, eluting with gradient 0-50% acetonitrile-water containing 0.1% trifluoroacetic acid to afford a mixture of 8-benzyloxy-5-[R-2-(1S,2S-2-cyclohexylcyclopentylamino)-1-hydroxy-ethyl]-1H-quinolin-2-one and 8-benzyloxy-5-[R-2-(1R,2R-2-cyclohexyl-cyclopentylamino)-1-hydroxy-ethyl]-1H-quinolin-2-one. δ_H 0.90-2.0 (m 18H), 2.50-3.10 (m 3H), 5.0-5.10 (m 1H), 5.12 (s 2H), 6.60 (d J 6 1H) 6.90-7.40 (m 7H), 8.02 (m 1H), 9.10 (br s 1H)

(b) These compounds are deprotected using the procedure described in Example 1(c) to yield a mixture of 5-[R-2-(1S,2S-2-cyclohexylcyclopentylamino)-1-hydroxyethyl]-8-hydroxy-1H-quinolin-2-one and 5-[R-2-(1R,2R-2-cyclohexylcyclopentylamino)-1-hydroxyethyl]-8-hydroxy-1H-quinolin-2-one (MH^+ 371).

Example 6

5-[R-2-(1R,2R-bicyclopentyl-2-ylamino)-1-hydroxyethyl]-8-hydroxy-1H-quinolin-2-one

(a) A mixture of 8-benzyloxy-5-R-oxiranyl-1H-quinolin-2-one (0.200 g, 0.68 mmol) and 1R,2R-bicyclopentyl-2-ylamine (Eur. J. Med. Chem., 2000, 35, 377; 0.209 g, 1.36 mmol) in

N,N-dimethylacetamide (2 ml) in a closed vial is irradiated in a CEM™ microwave reactor at 150 W (180°C) for 8 minutes. The crude product purified by reverse phase chromatography, eluting with gradient 0-50% acetonitrile-water containing 0.1% trifluoroacetic acid to afford 8-benzyloxy-5-[R-2-(1*R*,2*R*-bicyclopentyl-2-ylamino)-1-hydroxyethyl]-1*H*-quinolin-2-one. HPLC retention time 0.821 minutes.

(b) 8-Benzyloxy-5-[R-2-(1*R*,2*R*-bicyclopentyl-2-ylamino)-1-hydroxyethyl]-1*H*-quinolin-2-one (0.10 g, 0.22 mmol) and 10% Pd/C (50 mg) are suspended in methanol (4 ml) in a Radleys Carousel™ reaction station. The mixture is stirred under hydrogen atmosphere (0.35 bar) for 2 hours, the catalyst filtered on a Celite™ filter bed and washed with methanol. The combined filtrate and washings are evaporated and purified by MS directed preparative HPLC to afford 5-[R-2-(1*R*,2*R*-bicyclopentyl-2-ylamino)-1-hydroxyethyl]-8-hydroxy-1*H*-quinolin-2-one. MH^+ 357.

Example 7

5-[R-2-(1*R*,2*R*-2-Benzylcyclopentylamino)-1-hydroxyethyl]-8-hydroxy-1*H*-quinolin-2-one

(a) 1*R*,2*R*-2-Benzylcyclopentylamine is prepared using the procedure described in Eur. J. Med. Chem., 2000, vol 35, 377.

(b) 1*R*,2*R*-2-Benzylcyclopentylamine is reacted with 8-benzyloxy-5-*R*-oxiranyl-1*H*-quinolin-2-one using the procedure described in Ex. 7(a) to yield 5-[R-2-(1*R*,2*R*-2-benzylcyclopentylamino)-1-hydroxyethyl]-8-benzyloxy-1*H*-quinolin-2-one. HPLC retention time 0.843 min.

(c) 5-[R-2-(1*R*,2*R*-2-Benzylcyclo-pentylamino)-1-hydroxy-ethyl]-8-benzyloxy-1*H*-quinolin-2-one is deprotected using the procedure described in Example 7(b) to yield 5-[R-2-(1*R*,2*R*-2-benzylcyclopentylamino)-1-hydroxyethyl]-8-hydroxy-1*H*-quinolin-2-one, MH^+ 377.

Examples 8 to 14

The compounds of these Examples are prepared using procedures that are analogous to those described in Examples 1 to 7 respectively except using 7-benzyloxy-5-*R*-oxiranyl-3,4-dihydro-1*H*-quinolin-2-one in place of 8-benzyloxy-5-*R*-oxiranyl-1*H*-quinolin-2-one.

Examples 15 to 20

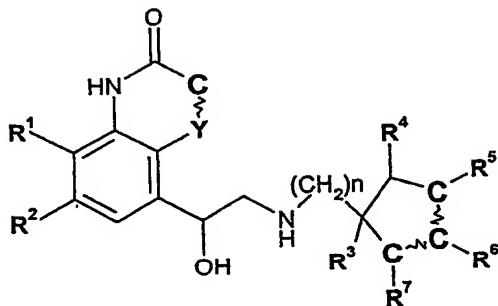
The compounds of these Examples are prepared using procedures that are analogous to those described in Example 1.

Examples 21 to 26

The compounds of these Examples are prepared using procedures that are analogous to those described in Example 1 except using 7- benzyloxy-5-R-oxiranyl-3,4-dihydro-1H-quinolin-2-one in place of 8-benzyloxy-5-R-oxiranyl-1H-quinolin-2-one.

CLAIMS

1. A compound of formula I



in free or salt or solvate form, where

-C₂-Y- denotes -CH=CH-, -CH₂-CH₂- or -CH₂-O-;

C=C denotes C=C or CH-CH;

one of R^1 and R^2 is hydroxy and the other is hydrogen;

n is an integer from 0 to 4;

R₃ is hydrogen or C₁-C₁₀-alkyl optionally substituted by a C₃-C₁₅-carbocyclic group or by

$\text{C}_1=\text{C}_1\text{a}=\text{alkoxy:}$

R⁴ is hydrogen, hydroxy, C₁-C₁₀-alkyl or C₁-C₁₀-alkoxy;

R^5 and R^6 are independently hydrogen, halo, a C_3 - C_{15} -carbocyclic group, a 5- or 6-membered heterocyclic ring wherein at least one of the ring atoms is nitrogen, oxygen or sulphur, C_1 - C_{10} -alkyl optionally substituted by a C_3 - C_{15} -carbocyclic group, or C_1 - C_{10} -alkoxy optionally substituted by a C_3 - C_{15} -carbocyclic group,

or R^5 and R^6 together form a C_3 - C_{10} -cycloalkyl or C_3 - C_{10} -cycloalkenyl in either case

optionally substituted by C₁-C₁₀-alkyl or C₁-C₁₀-alkoxy; and

R⁷ is hydrogen, hydroxy, a C₃-C₁₅-carbocyclic group, C₁-C₁₀-alkyl optionally substituted by a C₃-C₁₅-carbocyclic group, or C₁-C₁₀-alkoxy optionally substituted by a C₃-C₁₅-carbocyclic group.

2. A compound according to claim 1, where

-C₂-Y- denotes -CH=CH-;

$C=C$ denotes $C\equiv C$ or CH_2-CH_2 ;

one of R^1 and R^2 is hydroxy and the other is hydrogen;

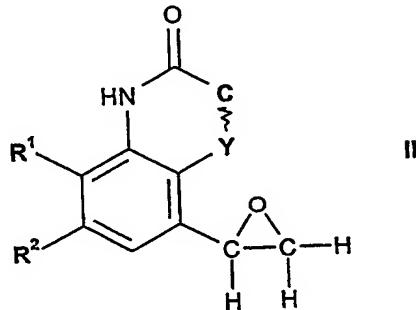
n is 0;

R^3 and R^4 are both hydrogen;

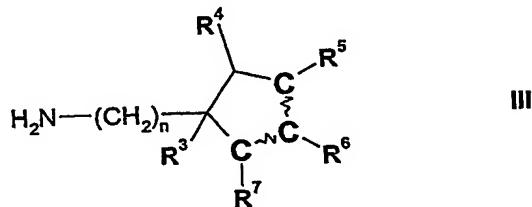
R^5 and R^6 are independently hydrogen or C_1 - C_{10} -alkyl,

9. A process for the preparation of a compound of formula I as defined in claim 1 in free or salt or solvate form comprising:

(i) reacting a compound of formula II



or a protected form thereof wherein -C-Y-, R¹ and R² are as defined in claim 1, with a compound of formula III



or a protected form thereof wherein C~C, R³, R⁴, R⁵, R⁶, R⁷ and n are as defined in claim 1; and

(ii) recovering the resultant compound of formula I in free or salt or solvate form.

EP 04 3516

